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### Gitelman syndrome

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# Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference



OPEN

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Gitelman syndrome (GS) is a rare, salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria. The disease is recessively inherited, caused by inactivating mutations in the *SLC12A3* gene that encodes the thiazide-sensitive sodium-chloride cotransporter (NCC). GS is usually detected during adolescence or adulthood, either fortuitously or in association with mild or nonspecific symptoms or both. The disease is characterized by high phenotypic variability and a significant reduction in the quality of life, and it may be associated with severe manifestations. GS is usually managed by a liberal salt intake together with oral magnesium and potassium supplements. A general problem in rare diseases is the lack of high quality evidence to inform diagnosis, prognosis, and management. We report here on the current state of knowledge related to the diagnostic evaluation, follow-up, management, and treatment of GS; identify knowledge gaps; and propose a research agenda to substantiate a number of issues related to GS. This expert consensus statement aims to establish

an initial framework to enable clinical auditing and thus improve quality control of care.

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KEYWORDS: hypokalemic metabolic alkalosis; hypomagnesemia; salt-losing tubulopathy; *SLC12A3*; thiazide-sensitive sodium-chloride cotransporter

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Gitelman syndrome (GS), also referred to as familial hypokalemia-hypomagnesemia, is a salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria.<sup>1,2</sup> With a prevalence at ~1 to 10 per 40,000, and potentially higher in Asia,<sup>3</sup> GS is arguably the most frequent inherited tubulopathy.<sup>4</sup> The disease is caused by biallelic inactivating mutations in the *SLC12A3* gene encoding the thiazide-sensitive sodium-chloride cotransporter (NCC) expressed in the apical membrane of cells lining the distal convoluted tubule.<sup>5</sup> To date, >350 mutations scattered throughout *SLC12A3* have been identified in GS patients.<sup>6,7</sup> The majority of patients are compound heterozygous for *SLC12A3* mutations, but a significant number of GS patients are found to carry only a single *SLC12A3* mutation.

The presence of both hypocalciuria and hypomagnesemia is highly predictive for the clinical diagnosis of GS, although hypocalciuria is highly variable and hypomagnesemia may be absent.<sup>1,8,9</sup> The use of clinical and biological features to differentiate from other salt-losing nephropathies is difficult

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in some cases. A GS-like phenotype, including hypomagnesemia and hypocalciuria, has also been associated with mutations in the *CLCNKB* gene encoding the chloride channel ClC-Kb, the cause of classic Bartter syndrome ([cBS] or Bartter syndrome type III). The localization of ClC-Kb in the distal convoluted tubule explains the phenotypic overlap with GS.<sup>10,11</sup> Genetic testing is increasingly available for GS, but it remains expensive.

GS has long been considered a benign tubulopathy, usually detected during adolescence or adulthood. Indeed, the condition may be asymptomatic or associated with relatively mild or nonspecific symptoms or both such as muscular weakness, fatigue, salt craving, thirst, nocturia, or cramps. However, this view has been challenged by reports emphasizing the phenotypic variability and potential severity of the disease.<sup>12</sup> Cruz *et al.*<sup>13</sup> showed that GS is associated with a significant reduction in the quality of life—similar to that associated with congestive heart failure or diabetes. Severe manifestations, such as early onset (before age 6 years), growth retardation, chondrocalcinosis, tetany, rhabdomyolysis, seizures, and ventricular arrhythmia have been described.<sup>13–15</sup> Of note, in many reports of severe complications, the diagnosis of GS was established on clinical rather than genetic grounds, potentially creating confusion with related disorders including cBS. Yet, phenotypic variability has also been documented in genetically confirmed GS patients, including in patients with identical *SLC12A3* mutations.<sup>16</sup> A combination of genotype, sex, modifier genes, compensatory mechanisms, as well as environmental factors or dietary habits might be involved in such variability.<sup>17</sup>

GS is usually managed by a liberal salt (NaCl) intake, together with oral magnesium and potassium supplements. Potassium-sparing diuretics, renin angiotensin system blockers including angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs are sometimes used. However, evidence supporting the efficacy, tolerability, and safety of these treatment options (either as standalone therapy or in combinations) in GS patients is limited. Information about long-term outcomes in GS is lacking. In particular, long-term consequences such as chondrocalcinosis, chronic kidney disease, secondary hypertension, and cardiac arrhythmias, and management during pregnancy need to be considered.

Despite the insights gained since its genetic elucidation in 1996, much mystery still surrounds GS. Further efforts are needed to substantiate issues including the following: diagnostic criteria and methods; clinical workup and follow-up; phenotypic heterogeneity; nature and severity of the biochemical abnormalities and clinical manifestations; and treatment and long-term consequences of the disease. Therefore, Kidney Disease: Improving Global Outcome (KDIGO) hosted a controversies conference to assess the current state of knowledge related to GS, identify knowledge gaps, and propose a research agenda. This report summarizes the guidance for clinical practice and future research developed at this conference by a global multidisciplinary panel of experts.

## Clinical characteristics and diagnosis

GS presents mainly in adolescents and adults but can also be encountered in children, as early as in the neonatal period.<sup>15,18</sup> The key clinical complaints and manifestations suggesting a diagnosis of GS (Table 1) include the following: salt craving (i.e., preference for salty food or a salted treat during childhood); muscle weakness, fatigue, limited sport performance or endurance; episodes of fainting, cramps, tetany, paresthesia, carpopedal spasms; growth retardation, pubertal delay, short stature; thirst or abnormal drinking behavior; episodes of abdominal pain. Dizziness, vertigo, polyuria, nocturia, palpitations, joint pain, and visual problems may be reported in adults.

The proposed biochemical criteria for suspecting a diagnosis of GS (Table 2) include the following: documented chronic hypokalemia (<3.5 mmol/l) concomitant with inappropriate renal potassium wasting (spot urine, potassium-creatinine ratio >2.0 mmol/mmol [>18 mmol/g]), in absence of potassium-lowering drugs; metabolic alkalosis; hypomagnesemia (<0.7 mmol/l [<1.70 mg/dl], [Supplementary Table S1]); inappropriate renal magnesium wasting<sup>19</sup> (fractional excretion of magnesium >4%);<sup>19,20</sup> hypocalciuria (spot urine, calcium-creatinine ratio <0.2 mmol/mmol [<0.07 mg/mg] in adults, [Supplementary Table S1]); normal ranges of calcium-creatinine ratio are different in children, [Supplementary Table S2]); high renin (activity or plasma levels); fractional excretion of chloride >0.5%; normal or low blood pressure; normal renal ultrasound with absence of nephrocalcinosis or renal abnormalities. If plasma electrolyte levels are normal or close to normal in a patient taking potassium or magnesium supplements or both, these supplements should be stopped for at least 48 hours in order to potentially unmask the abnormalities. Plasma and urine samples should be obtained concomitantly. No evidence supports the need for 24-hour urine collection; spot urine samples are usually sufficient to establish the diagnosis.

Arguments against the diagnosis of GS (Table 2) include the following: a family history of renal malformations or any

**Table 1 | Clinical manifestations encountered in Gitelman syndrome patients**

Most common (>50% of patients)	Prominent (20% to 50% of patients)	Occasional (<20%)	Rare (case reports)
Salt craving	Fainting	Early onset (before age 6)	Seizure
Cramps, muscle weakness	Polyuria	Failure to thrive	Ventricular tachycardia
Fatigue	Arthralgia	Growth retardation	Rhabdomyolysis
Dizziness	Chondrocalcinosis	Pubertal delay	Blurred vision
Nocturia	Prolonged QT interval	Vertigo, ataxia	Pseudotumor cerebri
Thirst, polydipsia	Febrile episodes	Carpopedal spasm, tetany	Sclerochoroidal calcifications
Paresthesia, numbness		Vomiting	
Palpitations		Constipation	
Low blood pressure		Enuresis	
		Paralysis	

Adapted, with permission, from Devuyst *et al.*<sup>83</sup>

**Table 2 | Diagnostic criteria for Gitelman syndrome**

## Criteria for suspecting a diagnosis of GS

- Chronic hypokalemia ( $<3.5$  mmol/l) with inappropriate renal potassium wasting (spot potassium-creatinine ratio  $>2.0$  mmol/mmol [ $>18$  mmol/g])
- Metabolic alkalosis
- Hypomagnesemia ( $<0.7$  mmol/l [ $<1.70$  mg/dl]) with inappropriate renal magnesium wasting (fractional excretion of magnesium  $>4\%$ )
- Hypocalciuria (spot calcium-creatinine ratio  $<0.2$  mmol/mmol [ $<0.07$  mg/mg]) in adults.<sup>a</sup>
- High plasma renin activity or levels
- Fractional excretion of chloride  $>0.5\%$ <sup>b</sup>
- Low or normal-low blood pressure
- Normal renal ultrasound

## Features against a diagnosis of GS

- Use of thiazide diuretics or laxatives
- Family history of kidney disease transmitted in an autosomal dominant mode
- Absence of hypokalemia (unless renal failure); inconsistent hypokalemia in absence of substitutive therapy
- Absence of metabolic alkalosis (unless coexisting bicarbonate loss or acid gain)
- Low renin values
- Urine: low urinary potassium excretion (spot potassium-creatinine ratio  $<2.0$  mmol/mmol [ $<18$  mmol/g]); hypercalciuria
- Hypertension,<sup>c</sup> manifestations of increased extracellular fluid volume
- Renal ultrasound: nephrocalcinosis, nephrolithiasis, unilateral kidneys, cystic kidneys
- Prenatal history of polyhydramnios, hyperechogenic kidneys
- Presentation before age 3 years<sup>c</sup>

## Criteria for establishing a diagnosis of GS

- Identification of biallelic inactivating mutations in *SLC12A3*

GS, Gitelman syndrome.

Listed are typical features arguing for or against a diagnosis of GS based on published evidence and collective clinical experience. Features in an individual patient may vary and ultimately the diagnosis rests on genetic testing. Thus, age of onset before 3 years of age has been reported, as has hypertension (in middle-aged and elderly patients with GS) and renal cysts.<sup>84</sup>

<sup>a</sup>Normal calciuria ranges are different in children due to lower creatinine excretion (see [Supplementary Table S2](#)).

<sup>b</sup>The value of fractional excretion of chloride is based on expert opinion (high variability of urinary chloride alone) and requires verification from published clinical observations.

<sup>c</sup>Hypertension and presentation before age 3 years do not exclude GS (see text).

kidney disease dominantly transmitted; the presence of a renal malformation (e.g., unilateral kidneys, polycystic kidneys, etc.); a history of polyhydramnios or hyperechogenic fetal kidneys; presentation before age 3 years; chronic use of diuretics or laxatives; lack of hypokalemia or inconsistent hypokalemia in absence of substitutive therapy; long history of hypertension; manifestations of increased extracellular fluid volume. Of note, the presence of arterial hypertension does not exclude the diagnosis of GS in adults.<sup>21,22</sup>

Confirmation of clinically suspected GS rests on genetic testing, which should be offered to all subjects. The diagnosis of GS is proven by identification of biallelic inactivating *SLC12A3* mutations. In view of the rapid progress of genetic testing, hydrochlorothiazide testing is no longer recommended as a diagnostic tool in GS because of the related risks: when it is used diagnostically (i.e., to differentiate from Bartter syndrome), there is a risk of acute volume depletion in subjects with loop of Henle defect.<sup>8</sup> Other limitations include testing in children or in patients taking medications affecting

tubular transport processes. Hydrochlorothiazide in general may also induce acute interstitial nephritis and hypersensitivity reactions. Unless specific manifestations (e.g., significant proteinuria) are encountered, a renal biopsy is not necessary for the diagnosis of GS.

The differential diagnosis of GS includes cBS. The latter is more likely when the presentation occurs at young age ( $<3$  years), with failure to thrive, polyuria, and normal plasma magnesium levels. However, cBS and GS may be clinically indistinguishable.<sup>10,11,23</sup> Mutations in the *HNF1B* gene encoding the transcription factor HNF1- $\beta$  can mimic the electrolyte abnormalities (particularly hypomagnesemia) encountered in GS. The presence of maturity onset diabetes of the young, early chronic kidney disease, family history compatible with a dominant mode of inheritance, abnormal liver enzymes, renal or urogenital malformations or kidney cysts should point to *HNF1B*-related disorders. *HNF1B* mutations can occur in the heterozygous state, either inherited or *de novo*, and comprise point mutations as well as whole gene deletions.<sup>24</sup> Approximately 50% of patients develop hypomagnesemia due to renal magnesium wasting, often accompanied by hypocalciuria, indicating that the distal convoluted tubule is involved.<sup>25</sup> Mutations in the *KCNJ10* gene coding for the inwardly rectifying potassium channel KCNJ10/Kir4.1 cause an autosomal recessive disorder characterized by epilepsy, ataxia, sensorineural deafness, and tubulopathy (or EAST syndrome). The extrarenal features of EAST syndrome allow it to be distinguished from GS.<sup>26</sup>

The differential diagnosis of GS also includes diuretic and/or laxative abuse, which is unusual in children, and chronic vomiting. Measurement of urinary chloride (e.g.,  $<25$  mEq/l for surreptitious vomiting) and a urine screen for diuretics (e.g., by mass spectrometry) can help exclude GS in these patients.<sup>27</sup> The association of hypokalemic metabolic alkalosis with hyperreninemic secondary aldosteronism is also found in other familial disorders affecting the kidneys or the gastrointestinal tract, or it can be acquired. For example, patients with cystic fibrosis are prone to develop episodes of hyponatremic, hypochloremic dehydration with metabolic alkalosis.<sup>28</sup> GS-like manifestations have been reported as a rare complication of the use of cisplatin.<sup>29</sup> Autoimmune disorders may cause renal tubular disorders, potentially due to autoantibodies against tubular components.<sup>30</sup> Typical features of GS have been associated with autoimmune disorders including iritis and arthritis<sup>31</sup> and Sjögren syndrome.<sup>32</sup>

Because of its rarity, GS may not be suspected as a distinct entity. As the clinical manifestations may be nonspecific, the disease is often discovered fortuitously during biochemical workup. The value of checking plasma potassium and magnesium levels in the workup of indirectly related conditions such as epilepsy, growth retardation, pubertal delay, and neuromuscular disorders should be stressed.

**Clinical manifestations and workup**

Most of the clinical problems in GS are linked to electrolyte disturbances, in particular chronic salt loss, hypokalemia, or



hypomagnesemia, or a combination of these. Increasing awareness of the disease is reflected by an increased number of patients identified, favoring the report of rare complications (Table 1) that should warrant the appropriate workup.

Because GS originates from the distal convoluted tubule, the salt and water losses in GS patients are less pronounced than in antenatal BS or cBS because urinary concentrating ability is largely intact. GS patients are often asymptomatic or present with symptoms such as muscle weakness, fatigue, salt craving, thirst, nocturia, constipation, cramps, carpopedal spasms, or tetanic episodes triggered by hypomagnesemia.<sup>33,34</sup> Blood pressure is typically low, particularly for patients with severe hypokalemia and hypomagnesemia.<sup>35</sup> Complications of GS include chondrocalcinosis<sup>36</sup> and sclerochoroidal calcifications.<sup>37</sup> This is because magnesium ions increase the solubility of calcium pyrophosphate crystals and are important activators for tissue-nonspecific alkaline phosphatase, which hydrolyzes pyrophosphates (PPi) into inorganic phosphate (Pi), hence hypomagnesemia may promote the formation of calcium pyrophosphate crystals in joints and sclera.<sup>38</sup> In addition, increased renal calcium reabsorption may contribute to calcium deposition, and patients with GS have higher bone mineral density, similar to chronic thiazide treatment, associated with a decreased rate of bone remodeling.<sup>39,40</sup> They may also present with growth retardation, pubertal delay, and short stature, reflecting an alteration in the growth hormone/insulin-like growth factor I axis or pleiotropic effects resulting from the biochemical disturbance.<sup>41</sup> Hypokalemic rhabdomyolysis has been reported in several GS patients.<sup>42</sup>

Ultrasound or X-ray examination should be performed in case of specific complaints that are suggestive of chondrocalcinosis. Ophthalmology examination is indicated when sclerochoroidal calcifications are suspected.<sup>37</sup>

Potassium and magnesium depletion prolong the duration of the action potential in cardiomyocytes, resulting in prolonged QT interval in ~50% of the patients, which could lead to an increased risk for ventricular arrhythmias.<sup>43,44</sup> GS patients who presented with long runs of ventricular tachycardia have been reported.<sup>14</sup> Given isolated reports on cardiac arrhythmias, long QT and sudden death in GS, an electrocardiogram (ECG) should be performed at rest to assess rhythm and QT duration. A further cardiology workup (e.g., Holter, stress ECG) is indicated where patients complain of palpitations or syncope, or if the ECG abnormalities persist despite attempted improvement of the biochemical abnormalities.<sup>45</sup>

Patients with GS may present glucose intolerance or insulin resistance or both secondary to chronic hypomagnesemia and hypokalemia.<sup>46</sup> Nevertheless, increased insulin sensitivity and protection from atherogenesis due to blunted angiotensin II signaling and reduced oxidative stress have also been reported.<sup>47,48</sup>

Reports suggest that GS may be associated with glomerular proteinuria due to abnormalities of the glomerular basement

membrane.<sup>22,49</sup> Chronic kidney disease might develop in GS patients due to either chronic hypokalemia, which is associated with tubulointerstitial nephritis, tubule vacuolization, and cystic changes, or volume depletion and increased renin-angiotensin-aldosterone, which may contribute to renal damage and fibrosis.<sup>21,50,51</sup>

Many patients with GS present with abdominal pain, which may be due to intestinal paresis because of hypokalemia or intolerance of potassium and magnesium supplementation. These complaints should be investigated appropriately and treated accordingly. Impaired renal phosphate handling<sup>52</sup> has also been reported.

### Genetic testing

The detection of biallelic inactivating *SLC12A3* mutations is crucial for the diagnosis of GS. The analytical sensitivity (i.e., the proportion of positive tests if 2 mutations in the *SLC12A3* exons or exon-intron boundaries are present) and specificity (i.e., proportion of negative tests if 2 mutations in *SLC12A3* are not present) of genetic testing for GS is 90% to 100% and 100%, respectively. Because there are GS patients who do not have 2 mutations in *SLC12A3* (i.e., a mutation in the noncoding regions or in another gene, which are not included in the test), the clinical sensitivity (proportion of positive tests if the disease is present) is 65% to 80%, depending on the genetic methods used.<sup>7,12,50,53–55</sup> Pathogenic *SLC12A3* mutations include larger rearrangements (deletions), which can be picked up by multiplex ligation-dependent probe amplification,<sup>7</sup> and intronic mutations, which can be screened for by cDNA analysis of lymphocytes.<sup>50,56</sup> As genetic testing becomes more accessible and comprehensive, it should be offered to all patients with a clinical suspicion of GS (minimal criteria). It should be performed in a laboratory accredited for diagnostic genetic testing.

The use of a next generation sequencing–based gene panel to parallel sequence (in 1 test) all genes that are relevant in the differential diagnosis of GS is recommended. Different next generation sequencing gene panels are available; it should at least include the *SLC12A3*, *CLCNKB*, and *HNF1B* genes. If only a single variant has been identified by next generation sequencing panel sequencing, the analysis should be complemented with a test for a deletion (multiplex ligation-dependent probe amplification) on the other allele. If Sanger sequencing is the only available technique in the diagnostic lab, sequential testing of *SLC12A3*, *CLCNKB*, and *HNF1B* should be performed, and if necessary complemented by multiplex ligation-dependent probe amplification testing for these genes.

It must be kept in mind that in 15% to 20% of patients,<sup>7,57</sup> even after multiplex ligation-dependent probe amplification analysis, only 1 pathogenic mutation is discovered.<sup>7</sup> In these cases, mutations in regulatory regions including introns of *SLC12A3* or in another gene might be the underlying second molecular defect. At present, these mutations are only searched for in specific cases (e.g., severe cases, Asian background, genetic counseling purposes), but this may change with dissemination of next generation sequencing techniques in diagnostic labs.

Genetic counseling should be offered to any patient with GS and to parents with a young child suffering from the disease. This counseling could discuss testing of parents, siblings and partner. Prenatal diagnosis and preimplantation genetic diagnosis are technically feasible when 2 pathogenic *SLC12A3* mutations have been identified. In our experience, these tests have not been asked for because of the good prognosis in the majority of GS patients. In very severe cases, the possible use of these predictive tests could be potentially discussed.

In the near future, whole exome sequencing and whole genome sequencing, followed by targeted analysis, will become the genetic tests of preference in many patients with a presumed genetic disorder. Careful genetic counseling and specific informed consent should always precede those genetic screening tests.<sup>58</sup> It is important to note that with the increasing availability of new-population-based genetic data and functional studies, the classification of variants may change: the pathogenicity of previously disease-associated genetic variants could be questioned and, vice versa, variants of previously unknown significance could be confirmed as pathogenic.<sup>59</sup> Diagnostic laboratories should take into account the evolving population and consider *in vitro* studies to interpret patient results appropriately.<sup>60</sup>

### Treatment

Because GS is caused by a primary defect in a sodium-chloride cotransporter, *ad libitum* NaCl intake should be strongly advocated. We recommend to encourage patients to follow their propensity for salt consumption. As yet, the potential benefit of pharmacological NaCl supplements added to liberal salt intake has not been tested.

Individualized lifelong oral potassium or magnesium supplementation or both is the mainstay of treatment for patients with GS. In the presence of hypomagnesemia, magnesium supplementation should be considered first, because magnesium repletion will facilitate potassium repletion and reduce the risk of tetany and other complications.<sup>19,33</sup>

Many symptoms are improved by potassium or magnesium supplementation or both, but there is no evidence correlating the severity of blood levels with the intensity of symptoms. A reasonable target for potassium may be 3.0 mmol/l and magnesium 0.6 mmol/l (1.46 mg/dl). Achieving these targets can be difficult in some patients and supplementation with large doses may result in serious side effects including gastric ulcers, vomiting, or diarrhea with worsening biochemistries. An individual balance between improvement in blood values and side effects should be established. Realistic target values may be lower for some patients and may also change with time. Adherence to the supplementation may be influenced by cost—because variable reimbursement policies exist in different countries.

Potassium supplements should be given as chloride (KCl) because chloride is the main anion lost in the urine and patients are alkalotic. A starting dose of  $\geq 40$  mmol KCl (1–2 mmol/kg in children), in divided doses throughout the

day, is suggested. Potassium supplements should not be taken on an empty stomach to minimize gastrointestinal irritation or damage. KCl supplements can be administered in water, as syrup, or in a slow-release formulation according to each patient's preference. The dose will be titrated individually (side effects vs. symptoms), knowing that the maintenance dose may be high. Potassium-rich foods should be recommended, with the caution that some of them contain high carbohydrates and calories ([Supplementary Table S3](#)).

Intravenous KCl may be necessary either when the patient cannot take oral drugs or when the potassium deficit is very severe, causing cardiac arrhythmias, quadriplegia, respiratory failure, or rhabdomyolysis.<sup>61</sup> KCl should be diluted in saline, usually to a concentration of 40 mmol/l. In general, no more than 50 mmol/l should be given through a peripheral vein at a maximum rate of 10 mmol/h, because higher concentrations of potassium are very irritating, resulting in pain and sclerosis of the vein. For central venous lines, the maximum concentration is usually 80 mmol/l with a maximum rate of 20 mmol/h (depending on hypokalemia, ECG monitoring). Beyond 10 mmol/h, the patient should be monitored in a high-dependency environment or area. Severe hyperkalemia may develop when acute renal failure develops in a patient taking exogenous potassium supplementation.<sup>62</sup>

Oral administration of magnesium supplements is the preferred way to correct magnesium deficiency, which aggravates hypokalemia and renders it refractory to treatment by potassium.<sup>63</sup> All types of magnesium salts are effective, but their bioavailability is highly variable ([Supplementary Table S4](#)), resulting in osmotic diarrhea at high doses.<sup>64</sup> Organic salts (e.g., aspartate, citrate, lactate) have a higher bioavailability than magnesium oxide and hydroxide.<sup>64</sup>  $\text{MgCl}_2$  will also compensate the urinary loss of chloride. The recommended starting dose is 300 mg/day (12.24 mmol) of elemental magnesium (5 mg/kg in children, i.e., 0.2 mmol/kg), in slow-release tablets when possible. The supplementation should be divided into 2 to 4 doses, preferably with meals. Dosage titration based on blood levels and intestinal tolerance is usually necessary. Persistent diarrhea may mandate a drop in dosage, which paradoxically may improve serum levels thanks to increased bioavailability or decreased intestinal transit time or both.<sup>65</sup> A list of magnesium-rich foods is provided in [Supplementary Table S5](#).

Intravenous infusion of magnesium should be reserved either for patients presenting with acute, severe complications of hypomagnesemia (e.g., tetany, cardiac arrhythmias), or in cases of digestive intolerance to oral supplements. In cases of acute tetany, 20%  $\text{MgCl}_2$  should be administered intravenously (0.1 mmol Mg/kg per dose) and can be repeated every 6 hours.<sup>4</sup>

In cases of persistent, symptomatic hypokalemia when supplements are not sufficient despite adherence or when side effects are unacceptable or both, the use of potassium-sparing diuretics,<sup>66,67</sup> renin angiotensin system blockers,<sup>68</sup> or nonsteroidal anti-inflammatory drugs, such as indomethacin, or a combination of these have been proposed.<sup>69–71</sup> The

potassium-sparing diuretics amiloride, spironolactone, potassium canrenoate, and eplerenone can be useful, both to increase serum potassium levels in patients resistant to supplements and to treat magnesium depletion that is worsened by elevated aldosterone levels.<sup>66</sup> The use of spironolactone is complicated by its antiandrogenic effects such as gynecostasia, hirsutism, erectile dysfunction, and menstrual irregularities, which are particularly difficult in adolescents and young adults. Eplerenone is a selective aldosterone antagonist, with significantly lower affinity for androgen, progesterone, and glucocorticoid receptors in comparison with spironolactone and has therefore no antiandrogenic side effects.<sup>72</sup> These drugs compound the renal salt wasting and should thus be started cautiously to avoid hypotension. Concomitant salt supplementation should be considered.

The use of renin angiotensin system inhibitors (angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers) has been occasionally reported in the treatment of GS.<sup>68</sup> These drugs also aggravate renal sodium wasting and increase the risk of symptomatic hypovolemia; they should be stopped in case of acute, salt-losing complications, such as vomiting or diarrhea. Prostaglandin synthase inhibitors such as indomethacin are rarely used in GS, because urinary prostaglandin E2 levels in GS are usually normal. Refractory hypokalemia has also been treated with the specific COX-2 inhibitor rofecoxib,<sup>71</sup> but the use of this drug is limited by its long-term cardiovascular effects.

Recently, an open-label, randomized, crossover study was conducted to compare the efficacy and safety of 6-week treatment with once-daily doses of 75 mg slow-release indomethacin, 150 mg eplerenone, or 20 mg amiloride added to constant potassium and magnesium supplementation in 30 GS patients.<sup>73</sup> Each drug increased plasma potassium concentration by about 0.3 mmol/l. Amiloride and eplerenone aggravated sodium depletion, whereas indomethacin was associated with decreased estimated glomerular filtration rate and caused gastrointestinal intolerance in one-third of subjects. Despite a documented effect on hypokalemia, indomethacin and other nonsteroidal anti-inflammatory drugs should be used with caution due to their short- and long-term gastrointestinal side effects and nephrotoxicity.

A series of drugs should be avoided or used with caution in patients with GS (Table 3). These include drugs slowing sinus rhythm or influencing the QT interval (e.g., negative chronotropic drugs), drugs potentially exacerbating hypomagnesemia (e.g., proton-pump inhibitors, gentamicin, antiviral drugs), and acetazolamide.

The cornerstone of the prevention of chondrocalcinosis is magnesium supplementation. Both oral nonsteroidal anti-inflammatory drugs and low-dose oral colchicine are effective systemic treatments for acute chondrocalcinosis.<sup>74,75</sup> Nonsteroidal anti-inflammatory drugs have to be used with caution in GS due to risk of kidney injury, whereas colchicine treatment can increase the laxative effect of oral magnesium supplementation. Intra-articular corticosteroids may be considered in patients in whom other drugs are

**Table 3 | Drugs associated with hypokalemia and hypomagnesemia**

Site of loss	Drugs
<b>Hypokalemia</b>	
Shift from extracellular fluid to intracellular fluid compartment	β <sub>2</sub> -receptor agonists Insulin (high dose) with glucose Xanthines (theophylline, caffeine) Verapamil (in overdose) Sodium bicarbonate
Extrarenal	Laxatives
Renal	
Antimicrobials	Nafcillin, ampicillin, penicillin, aminoglycosides, amphotericin B, foscarnet
Diuretics	Acetazolamide Furosemide and other loop diuretics Thiazides Mannitol
Mineralocorticoids	Fludrocortisone
Antiepileptic	Topiramate
<b>Hypomagnesemia</b>	
Extrarenal	Proton pump inhibitor
Renal	
Antimicrobials	Drug-induced renal Fanconi syndrome: Aminoglycosides (gentamycin, streptomycin, tobramycin), pentamidine, amphotericin B, foscarnet, antiretroviral therapy
Diuretics	Furosemide Thiazide
Antitumoral	Cisplatin
Immunosuppressants	Tyrosine kinase inhibitors Calcineurin inhibitors (cyclosporine, tacrolimus) Mycophenolate Anti-EGF receptors (cetuximab, panitumumab)

EGF, epidermal growth factor.

See also Sung *et al.*<sup>85,86</sup>

contraindicated or not tolerated. Intermittent general corticosteroids, as well as methotrexate, have been proposed for patients with severe chondrocalcinosis.<sup>76</sup>

### Management and follow-up

The management of GS should be individualized, with appropriate change with time and demands. At least annual follow-up in a nephrology clinic to monitor potential complications and evolution is advocated. The symptoms may increase with aging, irrespective of the control of hypokalemia. The latter may be easier after menopause. Patients should be educated about side effects of the supplements, in particular abdominal pain and diarrhea induced by magnesium salts and gastric irritation from potassium chloride. Physicians also should be attentive to other factors that could hamper adherence to the supplements, including socioeconomic difficulties, lack of reimbursement, adolescence, transition period, work conditions, etc. The transition phase between pediatric and adult care is particularly important.

Long-term studies are needed to assess the natural history of GS and the individual risks of chronic hypokalemia and hypomagnesemia in terms of metabolic syndrome, cardiac arrhythmias, chronic kidney disease, blood pressure control,

and propensity to develop chondrocalcinosis. To date, there is no evidence that GS affects life expectancy.

The known aggravation of hypokalemia and hypomagnesemia during pregnancy requires the early institution of a joint management plan involving nephrology and specialized obstetrics, as well as appropriate adaptations in the supplementation.<sup>77–79</sup> The outcome of mother and fetus of GS pregnancies described to date is favorable, with no cases of arrhythmia or other serious cardiac complication reported for either the mother or fetus.<sup>77,78</sup> Importantly, angiotensin receptor blockers and angiotensin-converting-enzyme inhibitors should be stopped during pregnancy because of significant fetal risks.<sup>80,81</sup> Monitoring of plasma electrolyte levels is advised during labor. After delivery, the treatment of the mother may return to baseline supplementation and follow-up.

Caution should be taken when patients with GS undergo anesthesia. Hypokalemia and hypomagnesemia can potentiate the effects of local and general anesthetic agents (e.g., neuromuscular blockade during general anesthesia and adrenalin use in regional blockade). There is no definitive evidence to suggest exact preoperative levels of potassium and magnesium that are safe. In the general population, the UK National Institute for Health and Care Excellence (NICE)-approved guidelines suggest aiming for potassium levels of  $\geq 3.0$  mmol/l and magnesium 0.5 mmol/l (1.22 mg/dl).<sup>82</sup>

The electrolyte disturbances in children with GS are associated with pubertal and growth delay.<sup>12</sup> If growth failure is evident despite adequate supplementation, formal assessment of pubertal status and growth hormone levels is recommended. Treatment with growth hormone is likely to benefit those with true growth hormone deficiency if provided with optimized biochemical control.

Education about the cause and nature of the disease is critical for patient empowerment. This information can be provided through a variety of media, including personal education in a clinical setting; information leaflets; web-based information and patient-led forums (Supplementary Table S6); patient and family groups' support events. Patients, their caregivers or both need to know what to do in case of an emergency. A medical identity bracelet (e.g., Medic-Alert, <http://www.medicalert.org.uk/>) may be useful. If traveling, patients should carry a doctor's letter with them that lists medications required, and they must not be prevented from carrying adequate supplements for their journey in hand luggage. 'Sick day rules' are helpful in case of intercurrent illness (Supplementary Table S7). It is important to reexplain the disease at different stages of life to the young adult. Physicians at transition clinics should build up awareness and consciousness of the patient's disease and treatment and the implications thereof for daily life. Patients and their families should be encouraged to contact local or regional patient organizations (Supplementary Table S6).

GS can compromise school performance (e.g., absence, difficulty in concentration). Country-specific measures exist to compensate schooling limitations of these children. They

should be used or developed according to the local practice, on an individual basis.

GS can also compromise work performance. In larger companies, local occupational health physicians may aid patients in finding solutions for their specific health situations. For example, if fatigue makes working an 8-hour day impossible, accommodations might include extra rest periods, reduced hours, or the ability to work at home. Work shifts may be particularly difficult for GS patients. Patients may be afraid to disclose their condition because they fear losing their job. However, patients should be encouraged to share information about their disease, but not without providing the employer with educational resources about GS.

There is no evidence suggesting that participation in sports is deleterious in GS. Caution is recommended in cases of endurance or strenuous exercise or competition practice.

**Table 4 | Knowledge gaps and research questions for Gitelman syndrome**

#### Diagnostic and biomarkers

- Urinary exosomes, including assessment of NCC and pNCC
- Urine values or creatinine ratios establishing wasting for potassium, sodium, chloride (spot)
- Value of ionized versus total magnesium measurement

#### Clinical aspects

- Blood pressure control, hypertension (incidence, cause, etc.)
- Cardiovascular complications: conduction, myocardium, predictive effort ECG, reproducibility, age effect, QT interval, and electrolyte levels
- Metabolic complications: glucose tolerance, role of magnesium balance

#### Patient-related outcomes

- Quality of life, disability, sociology, perception of symptoms
- Disability scores
- Self-management techniques

#### Genetic aspects

- Genetic heterogeneity, causal genes, or modifier genes
- Assessment of the pathogenicity of variants
- Prevalence of *SLC12A3* mutations in exome database
- Effect of the carrier state, geographic variations
- Genotype-phenotype correlations, including effect of triple *SLC12A3* mutations
- Sex effect
- Establishing prevalence of the disease and the carrier state

#### Intervention

- Effect of high NaCl supplementation
- Effect of sport, increased muscular mass, potassium supplementation after exercise
- Define optimal target values for potassium and magnesium

#### Outcome and natural history

- Registry, biobanking
- Growth, activity, sports
- Glucose intolerance and metabolic profile
- Renal function, concentration defect, proteinuria, chronic kidney disease, cysts
- Cardiovascular complications
- Rare complications: pseudotumor cerebri, pectus excavatum, link with autoimmunity

#### Mother and child

- Pregnancy and fetal development

#### Monitoring

- Improve monitoring: noninvasive, frequency, possible transcutaneous measurements

ECG, electrocardiogram; NCC, thiazide-sensitive sodium-chloride cotransporter; pNCC, phosphorylated thiazide-sensitive sodium-chloride cotransporter.



Volume depletion in particular should be prevented, and additional salt or electrolytes or both may help. In cases of history of cardiac manifestations or prolonged QT, a cardiology workup is advised.

### Conclusion and perspectives

GS was first described in 1966, and its genetic basis was elucidated 30 years later. Despite a solid understanding of the underlying renal mechanism, the wide spectrum of clinical severity, ranging from incidental diagnosis in essentially asymptomatic patients to severe disability in others despite similar biochemical abnormalities, remains an enigma. A better understanding of the factors involved in this variability is critical to provide better treatments. Given the high numbers of incidental diagnoses, it is tempting to speculate that there may be significant underdiagnosis of GS. A list of identified knowledge gaps and proposals for a research agenda are provided in Table 4. As with essentially all rare diseases, support for evidence-based treatment in GS is limited at best. Most of the guidance provided in this conference output is based on clinical experience, observational studies or case reports and is therefore derived from low-grade evidence. We are fully aware that the guidance provided here will be revised with time. However, these recommendations represent our current state of knowledge and constitute an initial framework to enable clinical auditing and thus quality control for which future treatments can be compared and measured against.

### DISCLOSURE

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We dedicate this report to the memory of Dr. Alberto Bettinelli, a leading clinical researcher on Bartter and Gitelman syndromes.

### SUPPLEMENTARY MATERIAL

**Table S1.** Conversion table.

**Table S2.** Normal ranges of urinary calcium-creatinine ratio in children.

**Table S3.** Foods rich in potassium, with glucose, magnesium, and caloric content.

**Table S4.** Magnesium content by various salts.

**Table S5.** Foods rich in magnesium, with glucose, potassium, and caloric content.

**Table S6.** List of web resources for patients with Gitelman syndrome.

**Table S7.** Sick day rules.

Supplementary material is linked to the online version of the paper at [www.kidney-international.org](http://www.kidney-international.org).

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